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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/744,350 | 05/22/2001 | Francis X. Ignatious | 00537-181002 | 5160 |

37903 7590 05/19/2004

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| EXAMINER | |
|---|---|
| BORIN, MICHAEL L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1631 | |

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/744,350 | IGNATIOUS, FRANCIS X. | |
| | Examiner | Art Unit | |
| | Michael Borin | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17-32* is/are pending in the application.

4a) Of the above claim(s) *23,24,26,27 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-22,25,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Claims*

1. Amendment filed 01/30/2004 is acknowledged. Claims 33-48 are canceled. Claims 17-32 are pending. Claims 23,24,26,27,30-32 remain withdrawn from consideration. Claims 17-22,25,28,29 are being examined to the extent they read on the elected species: somatostatin analogue as a peptide, polylactide-co-glycolide containing COOH groups as a charged polyester, dichloromethane as an organic solvent, and sodium oleate as surfactant.

### *Claim Rejections - 35 USC § 103*

2. Rejection of claims 17-22, 28, 29 over Thompson et al. in view of Fong et al (US 4383975) is withdrawn. Examiner agrees that Thompson teaches dispersion of peptide in non-salt form in solution of polyester rather than dissolving peptide salt and polyester complex in organic solvent.

3. Claims 17-22, 28, 29 remain rejected under 35 U.S.C. 103(a) as obvious over Orsolini (US 5445832) in view of Shalaby (US 5672659), and further in view of Fong et al (US 4383975). The rejection is maintained for the reasons of record and further in view if the following.

Applicant argues that Orsolini employs a "suspension" of peptide in organic solvent rather than solution (as in instant method). Examiner disagrees. As can be seen from col. 3, lines 41-43, even though the reference addresses addition of peptide salt as "suspending", the resulting mixture is addressed as "solution" - see line 41: "solution is incorporated...". Further, even if it had been a suspension, the instant specification teaches that the polymer microspheres of the invention can be made by either suspending or dissolving - see p. 16, lines 14-17.

Further, applicant discusses "encapsulation efficiency" of method of Orsolini. However, applicant does compare the "encapsulation efficiency" of the reference with peptide content (% by weight content) used in the instant disclosure.

4. Claims 17-22, 28, 29 are rejected under 35 U.S.C. 103(a) as obvious over Herrmann et al (Eur. J. Pharm. Biopharm., 45, 75-82, 1988) in view of Shalaby (US 5672659) and Fong et al (US 4384975) .

The instant claims are drawn to oil-in-water method of preparing peptide-containing microcapsules comprising

- dissolving a salt of a peptide complexed with a charged polyester in an organic solvent to form a solution;
- dispersing the above solution in an aqueous solution containing surfactant;
- evaporating the organic solvent.

The elected species are: somatostatin analogue as a peptide, polylactide-co-glycolide containing COOH groups as a charged polyester, dichloromethane as an organic solvent, and sodium oleate as surfactant.

Herrmann et al review several methods of preparing somatostatin microspheres. One of the methods comprises dissolving somatostatin salt in organic solvent, adding the solution to polylactide-co-glycolide solution in dichloromethane, forming oil-in-water emulsion, and evaporating the organic solvent. See Fig. 1 ("co-solvent" method) and p. 77, left column. It is Examiner's understanding that the resulting solution presents solution of somatostatin complexed with a polylactide-co-glycolide in dichloromethane, i.e., it reads on the broad meaning of the first method step of the claimed method.

If, however, the claim is read more narrowly, as requiring to dissolve the existing complex of somatostatin with a polylactide-co-glycolide, it should be noted that the reference teaches that the order of mixing of the components does not change the either the result, obtaining clear solution in dichloromethane, or the efficiency of encapsulation (76%) - see p. 78, right column, lines 28-30). Therefore, it would be obvious to an artisan that the components can be added in any sequence. Further, as Shalaby et al (US 5672659) teach that complexing peptides (such as somatostatins) with polyesters has an advantage of control of releasing peptide from the conjugate *in vivo* (see col. 2, lines 40-46), one skilled in the art at the time the

invention was made would be motivated to use complexes of somatostatin and polyester in dichloromethane, rather than adding then sequentially as in Herrmann, because it provides an added benefit of being able to control of release of peptide *in vivo.*

In regard to surfactant used, although Orsolini does not teach sodium oleate as surfactant, the reference does teach that aqueous medium should contain an appropriate surfactant (col. 3, line 45). One would be motivated to use sodium oleate as a surfactant, because Fong et al (US 4384975) demonstrates that sodium oleate is an advantageous surfactant in preparing microparticles using oil-in-water process because it allow successful separation of microparticles due to stabilizing emulsion against uncontrolled agglomeration and coalescence during solvent removal. See col. 3, lines 10-14, col. 4, claim 9.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 17-22, 28, 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of making microcapsules comprising LHRH analogue of claim 26, does not reasonably provide enablement for making of microcapsules comprising other peptides (e.g., somatostatin). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims are drawn to method of making of microcapsules comprising a broad range of peptides. As pointed out by applicant, the limiting step of the method is obtaining solution, not suspension, of peptide and polyester in organic solvent. As Herrmann et al teach, "the suitability of a particular technique is mainly determined by the solubility of the peptide and drug which are usually fixed.... Depending on the solubility properties of the drug it can be either dissolved or dispersed..". See p. 76, left column. The only example demonstrating making of microcapsules as claimed and comprising the step of forming of a solution of peptide complex in dichloromethane describes making of microspheres of LHRH analogue. As for somatostatin microspheres, there is no evidence that they could be prepared by the same method; the specification describes making of somatostatin microspheres using different procedure (Example 2(d)). As argued by applicant, mixture of somatostain salt and polyester in dichloromethane described in Orsini (Examples 4,5) presents suspension rather than solution. Further, Shalaby (US 5672659) teaches

that the complexes of peptide (somatostatin, for example) with a charged polyester (i.e. complexes used in the instant invention; see specification, p. P. 19, bottom) should be dissolved in a water miscible organic solvent, such as acetone, rather than suggesting use of dichloromethane.

Therefore, insufficient guidance exist in the specification to enable a person of skill in the art to practice the invention without the need for undue experimentation.

***Prior art made of record***

6. Shalaby (US 5672659; the reference is used above as secondary reference in obviousness rejection) teaches method of preparing microparticles comprising dissolving the a peptide (somatostatin, for example) complexed with a charged polyester in an aprotic, water miscible organic solvent; mixing said organic solvent in water; and isolating said microparticles from water. See claims 29-31. The reference does not teach using dichloromethane as solvent and evaporating this solvent before isolating microparticles from water.

***Conclusion.***

7. No claims are allowed

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-

0713. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0549.

MICHAEL BORIN, PH.D
PRIMARY EXAMINER

May 6, 2004

mlb